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(54) Title: RECEPTORS			
(57) Abstract			
<p>The invention provides sequences which are novel splice variants of the chemokine receptor CXCR3, in particular an isolated nucleic acid molecule which comprises one of: a) the sequence set out in Fig. 1 (Seq.I.D.1), or the complementary strand thereof, b) a sequence which hybridises under stringent conditions to a sequence defined in a) above, or c) a sequence which, but for the degeneracy of the genetic code, would hybridise to a DNA sequence defined in a) or b) above and which sequence codes for a polypeptide having the same amino acid sequence as the amino acid sequence which would be encoded by the sequence to which it would be capable of hybridising or a fragment of variant thereof.</p>			

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RECEPTORS

The present invention relates to isolated nucleic acids which encode a chemokine receptor protein designated CXCR3b and to the receptor protein encoded by such nucleic acids.

Chemokines are a family of small cytokines that bring about the recruitment of leukocytes during inflammation. Two families of chemokines are termed CC or CXC chemokines based on the spacing of the first two cysteine residues they contain. Most CXC chemokines attract neutrophils, whereas CC chemokines are less selective and can attract monocytes, eosinophils, basophils and T-lymphocytes. All CC and CXC chemokine receptors are seven transmembrane G-protein coupled receptors and most are receptors for a number of chemokines although a number of specific chemokine receptor interactions exist. Such chemokine receptors are therefore an important target for the development of drugs which antagonise these receptors and thereby modulate inflammatory responses. The modulation of inflammatory responses is of therapeutic benefit in many conditions such as rheumatoid arthritis, psoriasis, multiple sclerosis, transplantation , delayed type hypersensitivity reactions, atherosclerosis and restenosis.

Loetscher, M. *et al.* (*J. Exp. Med.*, 184, 963-969 (1996)) describe the cloning of a human CXC receptor for two CXC chemokines (IP10 and Mig) which are secreted by monocytes. This receptor is referred to as either CXCR3 or CXCR3a. Unlike other known chemokine receptors, this receptor is expressed in activated, but not in resting T-lymphocytes. It may therefore play an important role in the selective recruitment of T-cells which occurs in T-cell mediated inflammatory conditions.

The present invention relates to a novel variant of this CXC receptor which is a splice variant resulting in the production of an altered amino terminus. The splice variant has been designated 'CXCR3b' and may have an altered pattern of tissue distribution and of function in the inflammatory process. The receptor is therefore particularly useful for identifying chemokines responsible for mediating inflammatory reactions via interaction

with CXCR3b and for identifying compounds liable to be capable of therapeutic benefit via agonism or antagonism of CXCR3b.

Therefore, according to the present invention, there is provided an isolated nucleic acid
5 molecule which comprises one of:

- a) the sequence set out in Fig. 1 (Seq. I.D.1), or the complementary strand thereof,
- b) a sequence which hybridises under stringent conditions to a sequence defined in a)
10 above, or
- c) a sequence which, but for the degeneracy of the genetic code, would hybridise to a DNA sequence defined in a) or b) above and which sequence codes for a polypeptide having the same amino acid sequence as the amino acid sequence which would be encoded by the
15 sequence to which it would be capable of hybridising or a fragment or variant thereof.

Preferably a DNA sequence of the present invention as described in b) above has the sequence given in Fig. 2 (Seq. I.D.3).

- 20 Also included in the scope of the present invention is any isolated RNA molecule capable of being encoded by a DNA molecule of the present invention.

There is also provided an isolated polypeptide which is coded by any of the nucleic acids of the present invention and which preferably has an amino acid sequence comprising the
25 sequence set out in Fig. 3 (Seq. I.D.2) and more preferably has the amino acid sequence of CXCR3b as set out in Fig. 4 (Seq. I.D.4) or a fragment or variant thereof.

- A fragment or variant polypeptide of the present invention is one which contains deletions,
30 insertions or alterations in the amino acid sequence but has substantially the same chemokine receptor activity as the polypeptide of which it is a fragment or variant.

There is also provided according to the present invention, nucleic acid vectors comprising a nucleic acid sequence of the present invention; cells containing a nucleic acid or vector of the present invention; purified antibodies reactive with a protein of the present invention; 5 cells expressing an antibody of the present invention; screens for antagonists or agonists of CXCR3b receptor comprising a nucleic acid, vector, protein, antibody or antibody producing cell of the present invention; and ligands capable of agonism or antagonism of a CXC3b receptor function.

10 Description of Figures:

Fig. 1 shows the DNA sequence of the novel exon of CXCR3b which encodes the amino terminal 14 amino acids of the receptor protein.

15 Fig. 2 shows the cDNA sequence encoding the CXCR3b receptor protein.

Fig. 3 shows the amino acid sequence of the novel amino terminal sequence of CXCR3b.

Fig. 4 shows the amino acid sequence of the CXCR3b receptor protein.

20 Nucleic acids and polypeptides of the present invention may be synthesised by known techniques and particularly by the methods described in the Examples hereto.

25 Nucleic acids of the present invention may be RNA or DNA molecules. A DNA molecule of the present invention may be genomic DNA, a synthetic oligonucleotide or more preferably is cDNA.

30 DNA sequences of the present invention which are characterised by their ability to hybridise under stringent conditions to sequences described herein may be identified by their ability to hybridise under conditions no less stringent than the following: hybridisation

would be performed at 65°C in 6XSSC (0.9M NaCl, 90mM tri-sodium citrate, pH 7.0),
10X Denhardts solution (0.2% BSA, 0.2% Ficoll, 0.2% polyvinylpyrrolidone) and
sonicated salmon sperm DNA at 100ug/ml. Washing would be carried out at 65°C in
6XSSC (0.9M NaCl, 90mM tri-sodium citrate, pH 7.0), 0.1% sodium dodecyl sulphate; or
5 an alternative hybridisation protocol defining the same level of stringency. The
hybridisation may suitably be probed with labelled oligonucleotides: 5'-CAGGG CTGGC
CCACA GC-3' and/or 5'-AGGGT CACCA CAGGG TTGG-3'.
The probe may be labelled with any suitable label but preferably ^{32}P may be used.
Further details about stringency conditions can be found in Current Protocols in Molecular
10 Biology (Ausubel, F.M. et al., eds., Vol. 1, Suppl. 26, 1991). Preferably, the degree of
hybridisation (i.e. the fraction of matched complementary nucleotide pairs) is at least 90%,
more preferably at least 95% and most preferably 100%.

Vectors, proteins, antibodies or antibody producing cells of the present invention may also
15 be produced by known techniques and like nucleic acids of the present invention may be
produced using techniques described in Sambrook, J., Fritsch, E.F. and Maniatis, T. (1989)
Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press,
Cold Spring Harbor, New York.

20 Proteins of the present invention (which term as used herein is intended to include
polypeptides and peptides) are preferably produced recombinantly from a nucleic acid of
the present invention but may also be purified proteins isolated from natural sources or may
be chemically synthesised.
25 The terms 'polypeptide' and 'protein' are used synonymously herein.

The terms 'isolated DNA', 'isolated RNA' or 'isolated polypeptide' molecules as used herein
is taken to mean that the relevant molecule is separated from at least one biological
component with which it would normally be associated in nature.

The present invention will now be illustrated by the following Examples which are in no way to be construed as limiting the scope of the present invention. The abbreviation 'PCR' used in the Examples means 'Polymerase Chain Reaction'.

5 **EXAMPLE 1**

Cloning of novel CXCR3 splice variants

PCR was performed on DNA prepared from a human lung cDNA library (Clontech QuickScreen). A primer specific for the CXCR3 sequence HPRB1 (5'-AGGAA GGTGT CGGTG CTGCT C-3'), was used in combination with a phage vector (λ gt10) specific primer F208 (5'-CCACA GATCT AGCAA GTTCA GCCTG GTTAA G-3').

10 Amplification was performed with a thermal profile of 94°C for 1 minute, then 35 cycles of 94 °C 30s, 65 °C 30s, 72 °C 1 min using a Taq and Pfu polymerase mix (Amersham). A nested reaction in which F208 was used first with HPR1 for 15 cycles and then with a 15 second CXCR3 specific primer HPR2 (5'-AGCGT GTCTG CTACA GTAGG TG-3') for a further 20 cycles also gave CXCR3b products. PCR products were purified (Promega Wizard PCR prep system) and ligated into the Eco RV site of pZero (Invitrogen). Recombinant plasmids were sequenced and searching of the Genbank database was performed using the GCG package.

20

EXAMPLE 2

Expression studies

25 The sites of the expression of the novel CXCR3b splice variant have been investigated. Primers were designed using the novel CXCR3a and b sequence to allow PCR reactions specific for the two variant forms to be carried out. PCR was performed using these primers on cDNA prepared from human tissues. Expression of both forms was detected in human Th1 and Th2 cells and also faintly in spleen. In all tissues analysed there appeared to be co-expression of both CXCR3 splice forms. Primers specific for the two CXCR3 30 splice variants were designed and used in RT-PCR reactions on cDNA prepared from

T-cells (Maxim Biotechnologies) and from human tissues (Origene). The primer pair SCM57 (5'-AGCCC AGCCA TGGTC CTTGA-3') and SCM59 (5'-CTGTA GAGGG CTGGC AGGAA TGCCA GGGCT-3') were used to amplify CXCR3a transcripts while SCM54 (5'-ATCAG GGGAA TGCCA GGGCT-3') and SCM56 (5'-TCGAA GTTCA GGCTG AAGTC-3') were used to specifically amplify CXCR3b transcripts. Amplification was carried out with a thermal profile of 94 °C 30s, 55 °C 30s, 72 °C 30s for 35 cycles using Taq polymerase (Advanced Biotechnologies).

C L A I M S

1. An isolated nucleic acid molecule which comprises one of :
 - 5 a) the sequence set out in Fig. 1 (Seq. I.D.1), or the complementary strand thereof,
 - b) a sequence which hybridises under stringent conditions to a sequence defined in a) above, or
 - 10 c) a sequence which, but for the degeneracy of the genetic code, would hybridise to a DNA sequence defined in a) or b) above and which sequence codes for a polypeptide having the same amino acid sequence as the amino acid sequence which would be encoded by the sequence to which it would be capable of hybridising or a fragment or variant thereof.
2. A nucleic acid molecule according to claim 1, wherein the nucleic acid is DNA.
15
3. A nucleic acid molecule according to claim 2, wherein the DNA is cDNA.
4. A nucleic acid vector comprising a DNA sequence as claimed in any one of claims 1 to 3.
20
5. A cell transformed with a vector as claimed in claim 4.
6. An isolated chemokine receptor encoded by a nucleic acid sequence as defined in any one of claims 1 to 3.
25
7. A method of identifying a ligand of a chemokine receptor as claimed in claim 6 which comprises combining a compound to be tested with a cell expressing the active receptor under conditions suitable for binding of ligand thereto, and detecting or measuring the formation of a complex between the compound and the receptor.
30
8. A method according to claim 7, wherein the ligand is an antagonist.

FIGURES

GAAAACCGGGGCATCAGGGAAATGCCAGGGCTGGCCCACAGCCCAGGGTACCCACAGGGTTGGGTGAGTGACCACCAAG

FIG. 1

GAAAACCGGGGCATCAGGGAAATGCCAGGGCTGGCCCACAGCCCAGGGTACCCACAGGGTTGGGTGAGTGACCACCAAG
TGCTAAATGACGCCAGGGTGGCGCCCTCTGGAGAACTTCAGCTTCTATGACTATGGAGAAAAGAGAGTGACTCGT
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GCCCTGGGCTGCCCAACCAACAGAGAGGGCTCCAGAGGCAGCCATCGTCTCCGCCGGATTCACTCTGGTCTGAGA

FIG. 2

MPGLAHSPGSPQGW

FIG. 3

MPGLAHSPGSPQGWVSDHQVLNDAEVAALLENFSSSYDYGENSESDSCCTSPPCPQDFSLNFDRALPALSLLFLGLLGNGAV
AAVLLSRRTALSSTDTFLLHLAVADTLLVLTPLWAVDAAVQWVFGSGLCKVAGALFNINFYAGALLACISFDRYLNIVHATQL
YRGPPARVTLTCLAVVGLCLLFALPDFIFLSAHHDERLNATHCQYNFPQVGRTALRVLQLVAGFLLPLLVMAYCYAHILAVLL
VSRGQRRLRAMRLVVVVVVAFALCWTPYHLVVLVDILMDLGALARNCRESRVDVAKSVTSGLGYMHCCLNPLLYAFGVK
FRERMWMILLRLGCPNQRGLQRQPSSRRDSSWSETSEASYSGL

FIG. 4

SEQUENCE LISTING

<110> DELANEY, STEPHEN (FOR US ONLY)
ASTRA PHARMACEUTICALS LIMITED
ASTRA AKTIEBOLAG (FOR MG ONLY)

<120> Receptors

<130> F 1943

<140>

<141>

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<170> PatentIn Ver. 2.0

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Pro Gln Gly Trp

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Pro Gln Gly Trp Val Ser Asp His Gln Val Leu Asn Asp Ala Glu Val
15 20 25

gcc gcc ctc ctg gag aac ttc agc tct tcc tat gac tat gga gaa aac 148
Ala Ala Leu Leu Glu Asn Phe Ser Ser Ser Tyr Asp Tyr Gly Glu Asn
30 35 40

gag agt gac tcg tgc tgt acc tcc ccg ccc tgc cca cag gac ttc agc 196
Glu Ser Asp Ser Cys Cys Thr Ser Pro Pro Cys Pro Gln Asp Phe Ser
45 50 55

ctg aac ttc gac cgg gcc ttc ctg cca gcc ctc tac agc ctc ctc ttt 244
Leu Asn Phe Asp Arg Ala Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe
60 65 70

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140 145 150

atc agc ttt gac cgc tac ctg aac ata gtt cat gcc acc cag ctc tac 532

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Gly Cys Pro Asn Gln Arg Gly Leu Gln Arg Gln Pro Ser Ser Ser Arg
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Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe Leu Leu Gly Leu Leu Gly
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Glu Thr Ser Glu Ala Ser Tyr Ser Gly Leu
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INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 99/00501
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A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 14/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC6: C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9725340 A1 (HUMAN GENOME SCIENCE, INC.), 17 July 1997 (17.07.97), see especially the seq. --	1-8
X	WO 9811218 A1 (THEODOR-KOCHER INSTITUTE), 19 March 1998 (19.03.98), see especially page 15, line 34 - page 16, line 5 -- -----	1-8

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Date of the actual completion of the international search

5 July 1999

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Telephone No. + 46 8 782 25 00

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01/06/99

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PCT/SE 99/00501

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9725340 A1	17/07/97	AU 4898496 A EP 0886643 A	01/08/97 30/12/98
WO 9811218 A1	19/03/98	AU 4260897 A	02/04/98